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Synthesis of Azasugars by Grignard Reaction on Glycosylamines

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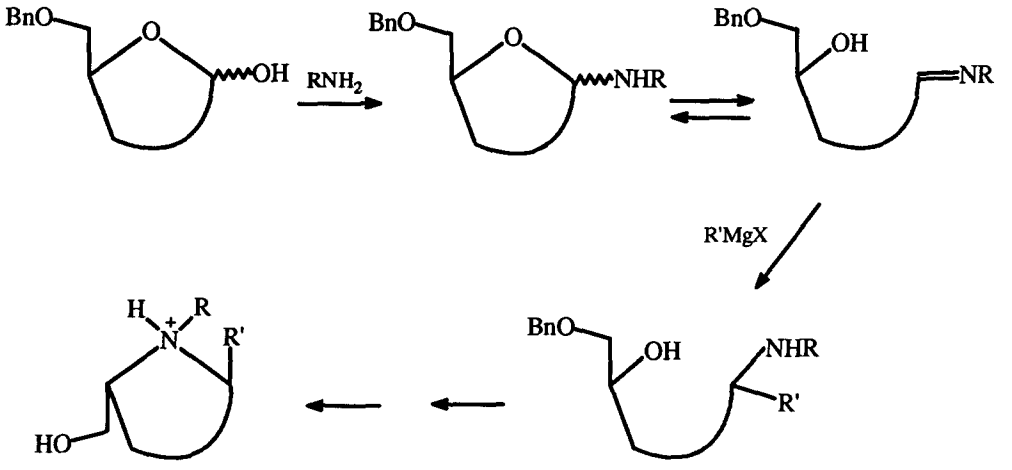
Abstract: Pyrrolidines **5a-b**, and piperidines **10a,b** and **15**, were synthesised by Grignard reaction on a glycosylamine, easily obtained from the parent sugar and a primary amine, followed by cyclization with triflic anhydride.

Azasugars, molecules structurally related to sugars in which the ring oxygen is replaced by an aminic nitrogen, have recently shown extremely promising pharmacological properties. These molecules are able to inhibit glycosidases since the protonated nitrogen can mime the oxonium ion which is the transition state intermediate in the enzymatic reaction. Some azasugars, such as 1-deoxynojirimicin and 1-deoxymannonojirimicin are able to inhibit the human lysosomial trimming α-glucosidases and α-mannosidases involved in the biosynthesis of the *N*-linked oligosaccharidic component of the membrane glycoproteins. It has been shown that this inhibition prevents *inter alia* the formation of the envelope glycoprotein of HIV[1] and the maturation of the oligosaccharide subunits of tumor cell glycoproteins which are correlated with malignant potential.[2]

These and other observations have stimulated an enormous effort in the synthesis of new azasugars and in the development of new synthetic procedures devoted to their synthesis. The main synthetic procedures till now described can be classified into the following general classes: 1) ex novo stereoselective building of the skeleton of the molecule by aldolase catalyzed condensation of dihydroxyacetone phosphate with an azidoaldehyde,[3] or by chemical methods,[4] 2) reductive amination of the anomeric centre of a sugar and subsequent cyclization,[5] 3) conversion of an hydroxy group of the sugar into an amino group and reduction of the obtained aminal,[6] 4) synthesis from non-carbohydrate chiral building blocks.[7]

In a preliminary communication[8] we described a new synthesis of new azasugars by reaction of 2,3,5-tri-*O*-benzyl-D-arabinose with different primary amines, stereoselective addition of a Grignard reagent to the so obtained arabinosylamine, and cyclization of the resulting aminoalcohol (Scheme 1). Starting with different sugars, and changing the primary amine and the Grignard reagent, a variety of pyrrolidines and piperidines can

be obtained, with virtually any different substituent at the nitrogen and at the adjacent carbon. The presence of alkyl substituents increasing the lipophilicity of the azasugar, can significantly improve the anti-HIV activity, as in the case of *N*-butyldeoxynojirimicin and 6-*O*-butanoylcastanospermine.[9] Furthermore it has been observed that *N*-alkylated deoxynojirimicins not only inhibit glucosidases in major extent than deoxynojirimicin does, but are also able to inhibit the glucosyltransferase catalyzed biosynthesis of glucosylceramide, which is not inhibited by deoxynojirimicin.[10]



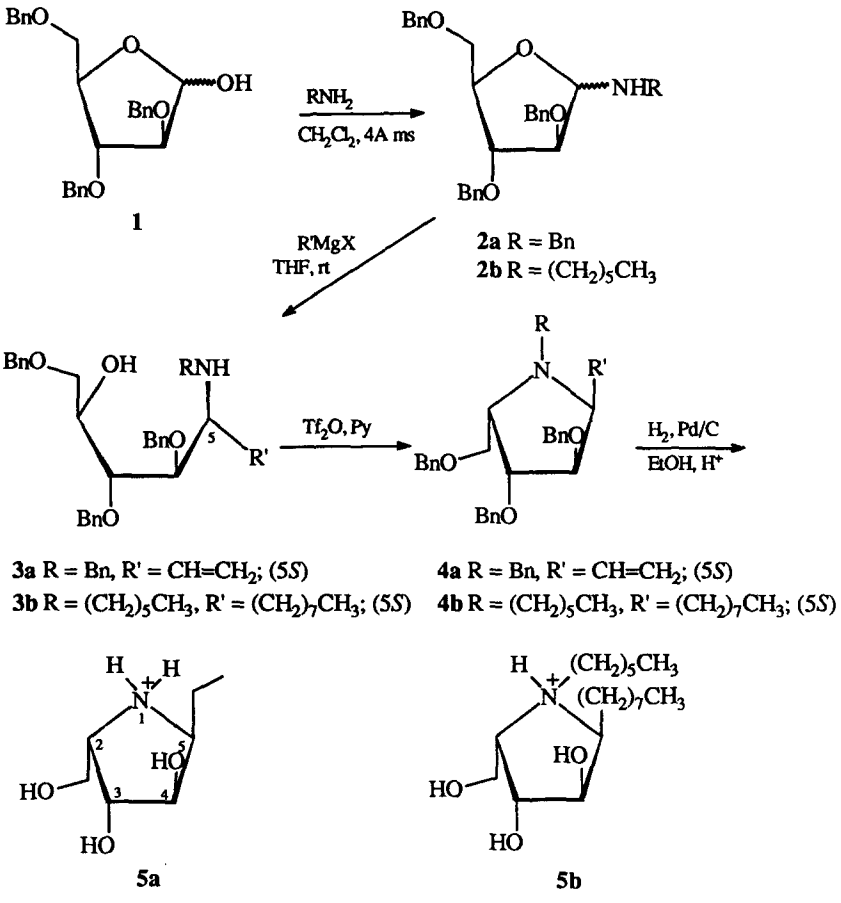
Scheme 1

We applied this procedure to different starting sugars, such as 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1**), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6a**), 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**6b**), and 2,3,4-tri-*O*-benzyl-D-ribopyranose (**11**), reacting with different amines and Grignard reagents (Scheme 2 and 3).

The aldose **1**, **6** or **11** dissolved in dry CH_2Cl_2, was reacted with an excess of the primary amine at room temperature to afford the corresponding glycosylamine **2**, **7** or **12**, which was directly submitted to the subsequent reaction. The glycosylamine **2a** is much less reactive towards an organometallic reagent than the corresponding aldose, allowing a better diastestereocontrol of the addition reaction. In fact, the reaction of vinylmagnesium bromide with 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1a**) occurs at -50 °C without an appreciable stereoselection,[11] while in the case of the *N*-benzyl-2,3,5-tri-*O*-benzyl-D-arabinofuranosylamine (**2a**) the reaction occurs at room temperature, affording stereoselectively the *threo* product in 88% d.e. The stereochemical outcome of the reaction was determined by mercuriocyclization of **3a** which afforded an α-*gluco*pyranosidic structure.[12] Treatment of the aminoalcohol **3a** with 1.5 equivalents of trifluoromethanesulfonic anhydride (Tf_2O) in pyridine at room temperature affords the cyclization product **4a** instead of the expected sulfonamide, which was not detected. This observation opened the way to an easy formation of azasugars following the sequence (a) glycosylamine formation, (b) Grignard reaction, and (c) cyclization with Tf_2O.

In order to extend this procedure first we changed the primary amine and the Grignard reagent.

Treatment of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1**) with hexylamine afforded crude *N*-hexyl-2,3,5-tri-*O*-benzyl-D-arabinofuranosylamine (**2b**), which was reacted with octylmagnesium bromide at room temperature. The *threo* product **3b** was obtained in 92% yield. No traces of the *erythro* isomer were detected by ^{13}C NMR and chromatography. Treatment of **3b** with Tf_2O gave the same interesting result observed for **3a**, the formation of azasugar **4b.**



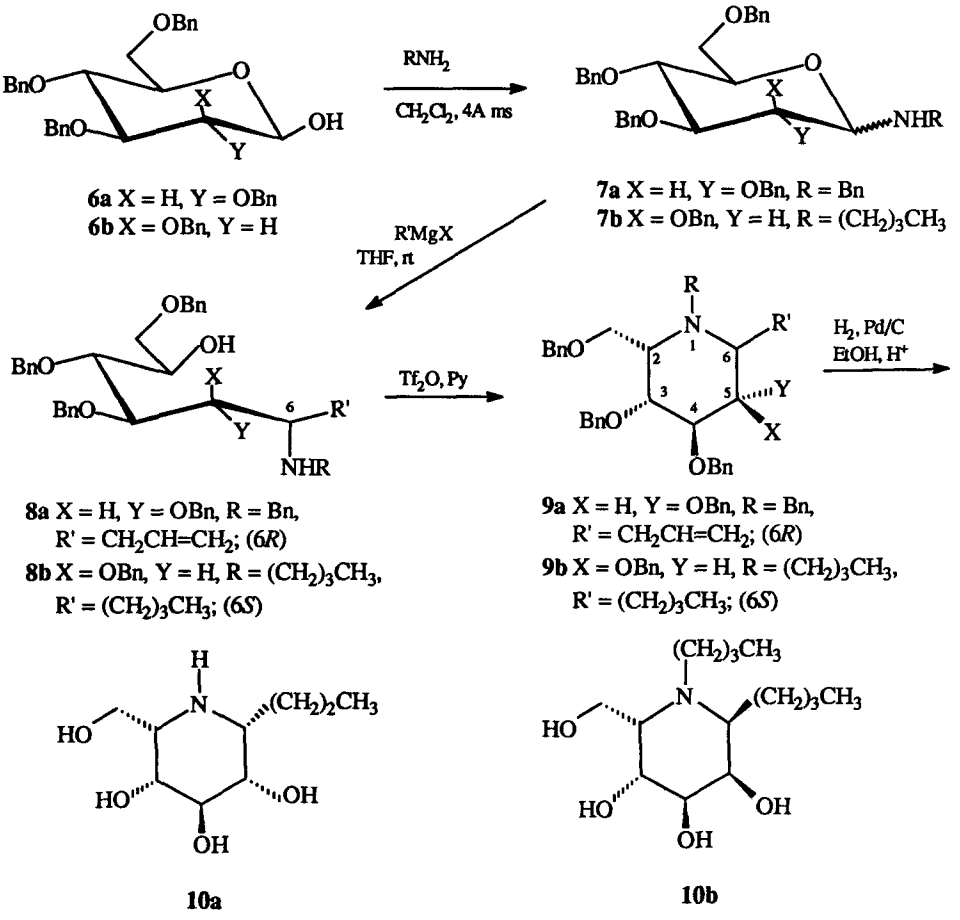
Scheme 2

The procedure can be easily extended also to the pyranoses (Scheme 3).

N-Benzyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylamine (**7a**) was reacted with allylmagnesium chloride affording the *threo* product **8a** stereoselectively (90% d.e. detected by ^{13}C NMR and HPLC of the crude product). Treatment of **8a** with Tf_2O, as described for **3a**, afforded the cyclization product **9a.**

The stereochemistry of the attack of the Grignard reagent on **7a** was determined on the cyclic product **9a**. The ^1H NMR of **9a** shows a 5.4 Hz axial-equatorial coupling constant between H-6 and H-5. Consequently the new stereocentre, formed in the Grignard reaction, has the *R* configuration, and the reagent attacks the imino function from the "re" face.

Finally, catalytic hydrogenation of **9a** afforded the azasugar **10a**.

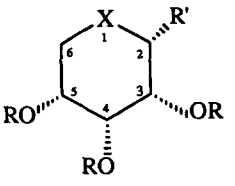


Scheme 3

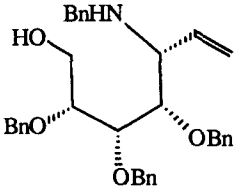
N-Butyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranosylamine (**7b**) reacted with butylmagnesium bromide affording the *threo* product **8b** stereoselectively. The *erythro* isomer was not detected by ^{13}C NMR and HPLC of the crude product. Also in this case the stereochemistry of the new chiral centre was determined after cyclization of **8b** to the piperidine **9b**. The ^1H NMR of **9b** shows a 4.3 Hz coupling constant between H-6 and H-5. This coupling constant is possible only if the new stereocentre has the *S* configuration (axial-equatorial

orientation of H-2 and H-3), as in the *R* isomer the hydrogens under investigation should assume an axial-axial orientation in a $^1C_4$ conformation. Catalytic hydrogenation of **9b** afforded the azasugar **10b**.

N-Benzyl-2,3,4-tri-*O*-benzyl-D-ribopyranose (**12**) reacted with vinylmagnesium bromide affording the *threo* product **13** stereoselectively. Cyclization with Tf_2O gave **14**, on which the stereochemistry of the new stereocentre was determined. In fact, the ^1H NMR of **14** shows a 5.5 Hz axial-equatorial coupling constant between the hydrogen of the new stereocentre (H-2) and the next one in the cycle (H-3). The ultimate azasugar **15** was then obtained by catalytic hydrogenation.



11 X = O, R = Bn, R' = OH
12 X = O, R = Bn, R' = NHBn
14 X = NBn, R = Bn, R' = CH=CH_2
15 X = NH, R = H, R' = CH_2CH_3



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Preliminary biological evaluations of the inhibition kinetics indicate that **5a**, **10a**, **10b** and **15** are poor competitive inhibitors of α-mannosidase from Jack Beans (K_i 1.2, 10.6, 4.0, and 6.3 mM respectively).

In conclusion, using the described procedure on different starting sugars, and employing different primary amines and Grignard reagents, one can obtain a variety of azasugars which differ for the structure and stereochemistry in the cycle and for the substituents at the nitrogen and at the adjacent carbon.

EXPERIMENTAL

Mass spectra were recorded on a VG 70-70 EQ spectrometer. UV spectra were recorded on a JASCO 7800 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC 300 and Varian XL 200 spectrometers, with TMS as internal reference, for solutions in $CDCl_3$, unless otherwise stated. The signals of the aromatic carbons in the ^{13}C NMR spectra are not reported. J values are given in Hz. $[\alpha]_D$ values were measured at 20°C on a Perkin-Elmer 241 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed with the flash procedure using Merck silica gel 60 (230-400 mesh). TLC was performed on Merck silica gel 60 F_{254} plates, developed with hexane-ethyl acetate in the ratio reported in brackets and visualised by spraying with a solution containing H_2SO_4 (31 ml), ammonium molibdate (21 g) and $Ce(SO_4)_2$ (1 g) in water (500 ml) and then heating at 110°C for 5 min.

Inhibition Study. 60 μL of a commercially available suspension of α-mannosidase from Jack Beans (Sigma) was diluted to 1000 μL with NaOAc-PIPES buffer solution (pH 6.5);[13] the amount (60 μL) of this solution added in each assay was chosen so that less than 10% of the substrate would be consumed in 45 s. To a 1 mL disposable cuvette, NaOAc-PIPES buffer solution (in the exact amount required to obtain 1000 μL of final volume), the inhibitor (200-700 μL of a 20 mM solution in NaOAc-PIPES buffer), and *p*-nitrophenyl α–mannoside (Fluka) (40, 100, 200 and 400 μL of a 10 mM solution in NaOAc-PIPES buffer) were added. The reaction of hydrolysis of the *p*-nitrophenyl α-mannoside was started by adding 60 μL of the solution of α–mannosidase, and the formation of the *p*-nitrophenate was monitored continuously at 400 nm for 45 s to calculate the initial hydrolysis rate. The same procedure was repeated with four different concentrations of each inhibitor (ranging from 2 to 7 mM), and the corresponding Lineweaver-Burk plot were calculated.

(2*R*,3S,4*R*,5*S*)-5-Benzylamino-1,3,4-tribenzyloxyhept-6-en-2-ol (3a). To a stirred solution of 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**1a**) (5.48 g, 13.04 mmol) in dry CH_2Cl_2 (30 ml), containing 4Å molecular sieves, the benzylamine (10 eq) was added. After the reaction was complete (4 days, monitoring by TLC), the reaction mixture was filtered on a Celite pad, the solvent and the excess of amine were evaporated under reduced pressure. Recrystallization of the crude product from diethyl ether gave **2a** (5.48 g, 90%), which was submitted to the next reaction. M.p. 72-74°C. Anal. calcd. for $C_{33}H_{35}NO_4$: C, 77.77; H, 6.92; N, 2.75. Found: C, 77.43; H, 6.98; N, 2.29.

Under N_2 atmosphere, the glycosylamine **2a** (1.00 g, 1.96 mmol) in dry THF (5 ml) was added to a solution of vinylmagnesium bromide (10 eq), previously prepared from alkyl halide and granulated magnesium in dry THF (10 ml). The reaction mixture was stirred overnight, quenched with NH_4Cl saturated solution; the organic layer was diluted with CH_2Cl_2 (50 ml), washed with 5% HCl (the minimum amount until the magnesium salts dissolved), $NaHCO_3$ saturated solution and water to neutrality, dried over anhydrous Na_2SO_4, filtered and evaporated. The reaction afforded a 94:6 mixture of diastereomeric products, as shown by the ^{13}C NMR of the crude reaction mixture (60.12 and 61.08 ppm for C-5), from which **3a** (866 mg, 82%) was isolated by chromatography (75:25). Oil, $[\alpha]_D$ +12.3 (*c* 1, $CHCl_3$). ^1H NMR: δ 3.62 (dd, 1H, H-5, $J_{5,6}$ = 8.8 Hz, $J_{4,5}$ = 1.4), 3.72 (d, 1H, PhCHN, J = 12.6), 3.77-3.88 (m, 3H, H-4, H-1a, H-1b), 3.92 (d, 1H, PhCHN, J = 12.6), 4.03 (dd, 1H, H-3, $J_{2,3}$ = 6.5, $J_{3,4}$ = 4.1), 4.16 (m, 1H, H-2), 4.57 (d, 1H, PhCHO, J = 11.5), 4.61-4.75 (m, 4H, 2 $PhCH_2O$), 4.83 (d, 1H, PhCHO, J = 11.5), 5.30 (dd, 1H, H-7a, $J_{6,7a}$ = 17.6, $J_{7a,7b}$ = 1.5), 5.38 (dd, 1H, H-7b, $J_{6,7b}$ = 10.0, $J_{7a,7b}$ = 1.5), 5.93 (ddd, 1H, H-6, $J_{6,7b}$ = 10.0, $J_{6,7a}$ = 17.6, $J_{5,6}$ = 8.8), 7.40 (m, 20H, PhH). ^{13}C NMR: δ 51.54 ($PhCH_2N$), 60.31 (C-5), 71.43 (C-4), 72.58, 73.57, 74.02, 74.48 (3 $PhCH_2O$, C-1), 78.01 (C-3), 83.75 (C-2), 118.44 (C-7), 138.91 (C-6). Anal. calcd. for $C_{35}H_{39}NO_4$: C, 78.18; H, 7.31; N, 2.60. Found: C, 78.15; H, 7.37; N, 2.72.

(2*S*,3*R*,4*R*,5*S*)-*N*-Benzyl-2-benzyloxymethyl-3,4-dibenzyloxy-5-ethenylpyrrolidine (4a). The aminoalcohol **3a** (4.55 g, 8.47 mmol), dissolved in dry pyridine (20 ml), was treated with trifluoromethanesulphonic anhydride (Tf_2O; 1.5 eq) under N_2 atmosphere. After 90 min. the reaction was complete, the reaction mixture was diluted with ethyl acetate (50 ml) and washed with water (2×50 ml); the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. Column chromatography (8:2) afforded **4a** (3.05 g, 70%). Oil, $[\alpha]_D$ -28.6 (*c* 1, $CHCl_3$). ^1H NMR: δ 3.39 (m, 1H, H-2), 3.55 (dd, 1H, H-5, $J_{5,1''}$ = 9.8, $J_{4,5}$ = 3.5), 3.72 (d,

1H, PhCHN, J = 14), 3.80 (m, 2H, H-1'a, H-1'b), 3.97 (d, 1H, PhCHN, J = 14.0), 4.30 (m, 2H, H-3, H-4), 4.46 (d, 1H, PhCHO, J = 11.5), 4.53 (s, 2H, $PhCH_2O$), 4.62 (d, 1H, PhCHO, J = 11.5), 4.66 (s, 2H, $PhCH_2O$), 5.16 (dd, 1H, H-2"a, $J_{2"a,2"b}$ = 1.7, $J_{2"a,1"}$ = 17.1), 5.31 (dd, 1H, H-2"b, $J_{2"a,2"b}$ = 1.7, $J_{2"b,1"}$ = 9.8), 5.90 (ddd, 1H, H-1", $J_{1",2"a}$ = 17.1, $J_{1",2"b}$ = 9.8, $J_{1",5}$ = 9.8), 7.30 (m, 20H, PhH). ^{13}C NMR: δ 52.64 ($PhCH_2N$), 60.33 (C-4), 66.33 (C-1'), 69.14-74.01 (3 $PhCH_2O$), 83.88 (C-3), 85.06 (C-2), 119.80 (C-1"), 136.12 (C-2"). Anal. calcd. for $C_{35}H_{37}NO_3$: C, 80.89; H, 7.18; N, 2.70. Found: C, 79.34; H, 6.65; N, 3.05.

(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-5-ethyl-2-hydroxymethylpyrrolidine (5a). A solution of **4a** (100 mg) in MeOH (3 ml) and HCl 2N (1 eq) was hydrogenated in the presence of 10% Pd/C. The reaction was recovered by filtration on a Celite pad and evaporation of the solvent to dryness. The reaction afforded **5a**·HCl (38 mg, quantitative). M.p. 174 °C, $[\alpha]_D$ -1.2 (*c* 1, MeOH). ^1H NMR (CD_3OD): δ 1.05 (t, 3H, H-2", J = 7.6), 1.80 (m, 2H, H-1"), 3.63 (dt, 1H, H-5, $J_{4,5}$ = 3.0, $J_{5,1"}$ = 7.5), 3.79-3.95 (m, 3H, H-2, H-1'), 4.06 (bd, 1H, H-4, $J_{4,5}$ = 3.0), 4.18 (bs, 1H, H-3). ^{13}C NMR (CD_3OD): δ 11.62 (C-2"); 20.86 (C-1"); 59.71 (C-1'); 65.08 and 65.25 (C-2, C-5); 76.46 (C-3, C-4). Anal. calcd. for $C_7H_{16}ClNO_3$: C, 42.54; H, 8.16; N, 7.09. Found: C, 42.68; H, 8.48; N, 6.95.

(2*R*,3*R*,4*R*,5*S*)-5-Hexylamino-1,3,4-tribenzyloxytridecan-2-ol (3b). A solution of **1a** (5 g, 11.9 mmol) in dry CH_2Cl_2 (40 ml) containing 4Å molecular sieves, was treated for 36 hrs with hexylamine (10 eq). The reaction mixture was then filtered on a Celite pad, the solvent and the excess of amine were evaporated under reduced pressure to give crude **2b** (5.35 g) which was directly dissolved in dry THF (10 ml) and treated with octylmagnesium bromide (10 eq) in dry THF (40 ml). After 2 hours the reaction was quenched with NH_4Cl saturated solution, the organic layer was diluted with CH_2Cl_2 (30 ml), washed with 5% HCl (the minimum amount until the magnesium salts dissolved), $NaHCO_3$ saturated solution and water to neutrality. Then the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. Column chromatography (6:4) gave **3b** (6.77 g, 92%). Oil, $[\alpha]_D$ +41.7 (*c* 1, $CHCl_3$). ^1H NMR: δ 0.87 (t, 3H, J = 7.0, CH_3), 0.89 (t, 3H, J = 7.0, CH_3), 1.00-1.62 (m, 22H, 11 CH_2), 2.44 (m, 1H, H-1'a), 2.67 (m, 1H, H-1'b), 2.75 (m, 1H, H-5), 3.54 (d, 1H, H-4, $J_{3,4}$ = 4.3), 3.67 (dd, 1H, H-1a, $J_{1a,2}$ = 5.0, $J_{1a,1b}$ = 9.7), 3.72 (dd, 1H, H-1b, $J_{1b,2}$ = 4.2, $J_{1b,1a}$ = 9.7), 3.83 (d, 1H, H-3, $J_{2,3}$ = 7.0, $J_{3,4}$ = 4.3), 3.88 (m, 1H, H-2), 4.34 (d, 1H, PhCHO, J = 12.0), 4.47 (d, 1H, PhCHO, J = 11.6), 4.52 (d, 1H, PhCHO, J = 11.6), 4.54 (d, 1H, PhCHO, J = 12.4), 4.62 (d, 1H, PhCHO, J = 12.4), 4.68 (d, 1H, PhCHO, J = 12) 6.85 (m, 15H, PhH). ^{13}C NMR: δ 14.13 (2 CH_3); 22.68-31.89 (11 CH_2); 46.63 (C-1'); 55.78 (C-5); 72.17, 72.62 and 72.73 (3 $PhCH_2O$); 71.03, 76.39 and 79.63 (C-2, C-3, C-4). Anal. calcd. for $C_{40}H_{59}NO_4$: C, 77.75; H, 9.62; N, 2.27. Found: C, 77.78; H, 9.62; N, 2.26.

(2*S*,3*R*,4*R*,5*S*)-*N*-Hexyl-2-benzyloxymethyl-3,4-dibenzyloxy-5-octylpyrrolidine (4b). A solution of **3b** (1.01 g, 1.63 mmol) in dry pyridine (16 ml) was treated with Tf_2O (1.5 eq) under N_2 atmosphere. After 6 hrs the reaction was complete. The reaction mixture was diluted with ethyl acetate (30 ml) and washed with water (2×30 ml portions); the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. Column chromatography (8:2) afforded **4b** (698 mg, 71%). Oil, $[\alpha]_D$ -3.7 (*c* 1, $CHCl_3$). ^1H NMR: δ 0.95 (m, 6H, 2 CH_3), 1.20-1.60 (m, 22H, 11 CH_2), 2.59 (m, 2H, CH_2N), 3.09 (dt, 1H, H-5, $J_{5,4}$ = $J_{5,1"a}$ = 6.5, $J_{5,1"b}$ = 2.5), 3.39 (m, 1H, H-2), 3.50 (dd, 1H, H-1'a, $J_{1'a,1'b}$ = 9.7, $J_{1'a,2}$ = 4.1), 3.69 (dd, 1H, H-1'b, $J_{1'a,1'b}$ = 9.7,

$J_{1'b,2}$ = 5.1), 4.01 (t, 1H, H-4, $J_{3,4} = J_{4,5}$ = 6.5), 4.11 (t, 1H, H-3, $J_{3,4} = J_{3,2}$ = 6.5), 4.47-4.65 (m, 6H, 3 $PhCH_2O$), 7.3 (m, 15H, PhH). ^{13}C NMR: δ 14.11 (2 CH_3); 22.67-31.90 (11 CH_2); 49.13 (CH_2N); 60.99 and 62.03 (C-2, C-5), 67.40 (C-1'); 72.13, 72.59 and 73.31 (3 $PhCH_2O$); 83.45 and 83.54 (C-3, C-4). Anal. calcd. for $C_{40}H_{57}NO_3$: C, 80.09; H, 9.58; N, 2.33. Found: C, 80.06; H, 9.75; N, 2.73.

(2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-*N*-hexyl-5-octyl-2-hydroxymethylpyrrolidine (5b). Hydrogenation of **4b** (499 mg) in MeOH (5 ml) and HCl 2N (1 eq) with 10% Pd/C gave quantitatively **5b**·HCl (273 mg). The reaction was recovered by filtration on a Celite pad and evaporation of the solvent to dryness. Oil, $[\alpha]_D$ +22.7 (*c* 1, MeOH). The NMR spectra, recorded in CD_3OD and in CD_3OD + DCl, showed splitted signals, due to the chiral ammonium salt. The free amine, obtained by hydrogenation in neutral conditions (which requires a longer time) showed single signals in the ^{13}C NMR (CD_3OD): δ 11.89 (CH_3); 15.81 (CH_3); 20.95, 21.12, 23.95, 24.53, 24.79, 24.99, 26.20, 27.77, 27.99, 29.90, 30.42 (11CH_2); 51.45 (CH_2N); 55.68 (C-1'); 68.21 and 68.46 (C-2, C-5); 73.05 and 74.04 (C-3, C-4). Anal. calcd. for $C_{19}H_{40}ClNO_3$: C, 62.35; H, 11.02; N, 3.83. Found: C, 62.14; H, 11.30; N, 3.59.

(2*R*,3*R*,4*R*,5*S*,6*R*)-6-Benzylamino-1,3,4,5-tetrabenzyloxynon-8-en-2-ol (8a). 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (1 g, 1.85 mmol) was dissolved in dry CH_2Cl_2 (74 ml), treated with benzylamine (10 eq) in the presence of 4Å molecular sieves. The reaction was complete in two weeks (monitored by TLC); the reaction mixture was filtered on a Celite pad, the solvent and the excess of amine were evaporated under reduced pressure and the crude product **7a** (1 g) underwent directly the subsequent reaction.

A solution of **7a** (944 mg, 1.5 mmol) in dry THF (8 ml) was treated with allylmagnesium chloride (10 eq) in dry THF (5 ml). The reaction was stirred overnight, quenched with NH_4Cl saturated solution; the organic layer was diluted with CH_2Cl_2 (10 ml), washed with 5% HCl (the minimum amount until the magnesium salts dissolved), $NaHCO_3$ saturated solution (2×20 ml) and water (2×20 ml) to neutrality. Then it was dried over anhydrous Na_2SO_4, filtered and evaporated. The reaction afforded a 95:5 mixture of diastereomeric products, as shown by the ^{13}C NMR of the crude reaction mixture (58.99 and 57.90 ppm for C-6), from which **8a** (605 mg, 60%) was isolated by column chromatography (hexane/ethyl acetate/methanol = 8:2:0.1). Oil, $[\alpha]_D$ +16.5 (*c* 1, $CHCl_3$). ^1H NMR: δ 2.23 (dt, 1H, H-7a, $J_{7a,7b}$ = 13.5, $J_{7a,6} = J_{7a,8}$ = 7.2), 2.42 (dt, 1H, H-7b, $J_{7a,7b}$ = 13.5, $J_{7b,6} = J_{7b,8}$ = 6.5), 2.60 (m, 1H, H-6), 3.50 (dd, 1H, H-3, $J_{3,2}$ = 7.0, $J_{3,4}$ = 3.0), 3.52-3.63 (m, 2H, H-1a, H-1b), 3.62 (d, 1H, PhCHN, J = 13.9), 3.84 (dd, 1H, H-5, $J_{5,6}$ = 2.2, $J_{5,4}$ = 7.5), 3.90 (d, 1H, PhCHN, J = 13.9), 4.05 (m, 1H, H-2), 4.28 (dd, 1H, H-4, $J_{4,5}$ = 7.5, $J_{4,3}$ = 3.0), 4.38-4.90 (8H, 4 $PhCH_2O$), 4.95 (m, 2H, H-9a, H-9b), 5.58 (m, 1H, H-8), 7.35 (m, 20H, PhH). ^{13}C NMR: δ 35.93 (C-7); 51.78 (C-1); 57.90 (C-6); 71.43 (C-2); 72.41, 73.52, 74.10 75.18 and 75.18 (5 $PhCH_2O$); 78.80, 80.32 and 81.01 (C-3, C-4, C-5); 117.60 (C-9); 136.89 (C-8). MS/FAB, 672 (M^+). Anal. calcd. for $C_{44}H_{49}NO_5$: C, 78.66; H, 7.35; N, 2.08. Found: C, 78.84; H, 7.41; N, 2.15.

(2*S*,3*R*,4*R*,5*S*,6*R*)-*N*-Benzyl-2-benzyloxymethyl-6-(prop-2-enyl)-3,4,5-tribenzyloxypiperidine (9a). Compound **8a** (480 mg, 0.71 mmol), dissolved in dry pyridine (5 ml), underwent the cyclization with Tf_2O (1.5 eq). After 2 hrs the reaction was complete, the reaction mixture was diluted with ethyl acetate (5 ml) and washed with water (3×10 ml); the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated.

The crude product was purified by chromatography (95:5), giving **9a** (243 mg, 52%). Oil, $[\alpha]_D$ +6.1 (*c* 1, $CHCl_3$). ^1H NMR : δ 2.36 (ddd, 1H, H-1"a, $J_{1"a,1"b}$ = 13.8, $J_{1"a,2"}$ = 7.0, $J_{6,1"a}$ = 6.0), 2.50 (ddd, 1H, H-1"b, $J_{1"a,1"b}$ = 13.8, $J_{1"b,2"}$ = 7.0, $J_{6,1"b}$ = 6.0), 3.21 (ddd, 1H, H-6, $J_{5,6}$ = 5.4, $J_{6,1"a}$ = $J_{6,1"b}$ = 6.0), 3.52 (m, 1H, H-2), 3.64 (dd, 1H, H-5, $J_{5,6}$ = 5.4, $J_{4,5}$ = 8.8), 3.73 (m, 3H, H-4, H-1'a, H-1'b), 3.84 (dd, 1H, H-3, $J_{3,4}$ = 9.5, $J_{2,3}$ = 5.3), 4.07 (d, 1H, PhCHN, J = 15.0), 4.14 (d, 1H, PhCHN, J = 15.0), 4.47-4.82 (m, 8H, 4 $PhCH_2O$), 4.94 (d, 1H, H-3"a, $J_{2",3"a}$ = 9.5), 4.99 (d, 1H, H-3"b, $J_{2",3"b}$ = 16.6), 5.88 (ddt, 1H, H-2", $J_{2",3"b}$ = 16.6, $J_{2",3"a}$ = 9.5, $J_{1"a,2"}$ = $J_{1"b,2"}$ = 7.0), 7.35 (m, 25H, PhH). ^{13}C NMR: δ 34.49 (C-1"); 58.37 (C-1'); 59.74 and 60.46 (C-2 and C-6); 71.14, 73.37, 73.37, 73.93 and 75.73 (4 $PhCH_2O$, 1 $PhCH_2N$); 79.17, 80.66, 81.42 (C-3, C-4, C-5); 116.14 (d, C-2"); 139.29 (t, C-3"). MS/FAB, 654 (M^+). Anal. calcd for $C_{44}H_{47}NO_4$: C, 80.83; H, 7.25; N, 2.14. Found: C, 79.35; H, 7.25; N, 2.67.

(2*S*,3*R*,4*R*,5*S*,6*R*)-2-Hydroxymethyl-6-propyl-3,4,5-trihydroxypiperidine (10a). A solution of **9a** (140 mg) in a mixture of MeOH-ethyl acetate (1:1) was hydrogenated in the presence of HCl 2N (1 eq) and 10% of Pd/C. After recovering the reaction by filtration on a Celite pad and evaporation of the solvent, **10a**·HCl was obtained (43 mg, quantitative yield). Oil, $[\alpha]_D$ -15.5 (*c* 1, MeOH). ^1H NMR (CD_3OD): δ 0.95 (t, 3H, CH_3, J = 7.0), 1.36 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 3.42 (ddd, 1H, H-6, $J_{6,1"a}$ = 4.2, $J_{6,1"b}$ = 10.4, $J_{6,5}$ = 1.1), 3.51 (dt, 1H, H-2, $J_{2,1'a}$ = $J_{2,1'b}$ = 6.7, $J_{2,3}$ = 1.5), 3.85 (d, 2H, CH_2O, J = 6.7), 3.92 (m, 1H, H-5), 3.97 (m , 1H, H-3), 4.07 (t, 1H, H-4, J = 3.3). ^{13}C NMR (CD_3OD): δ 14.68 (CH_3); 19.75 (CH_2); 31.94 (CH_2); 56.88 and 58.81 (C-2, C-6); 61.41 (C-1'); 68.99, 69.74 and 69.74 (C-3, C-4, C-5). Anal. calcd for $C_9H_{20}ClNO_4$:C, 44.72; H, 8.34; N, 5.79. Found: C, 44.48; H, 8.61; N, 5.55.

(2*R*,3*R*,4*R*,5*R*,6*S*)-6-Butylamino-1,3,4,5-tetrabenzyloxydecan-2-ol (8b). A solution of 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose **6b** (3.80 g, 7.04 mmol) in CH_2Cl_2 dry (28 ml), containing 4Å molecular sieves, was aminated with butylamine (10 eq). After the reaction was complete (monitored by TLC) the reaction mixture was filtered on a Celite pad, the solvent and the excess of amine were evaporated under reduced pressure and the crude product **7b** (5.95 g) was submitted to the next reaction.

Under N_2 atmosphere, the glycosylamine **7b** in dry THF (35 ml) was treated with butylmagnesium bromide (10 eq) in dry THF (21 ml). The reaction was stirred overnight, quenched with NH_4Cl saturated solution; the organic layer was diluted with CH_2Cl_2 (50 ml), washed with 5% HCl, until magnesium salts dissolved, $NaHCO_3$ saturated solution (2×100 ml) and water (2×100 ml) to neutrality. Then it was dried over anhydrous Na_2SO_4, filtered and evaporated. The crude product, analysed by ^{13}C NMR and HPLC (Merck LiChrosorb Si 60, 6:4) showed the presence of only one diastereomeric product **8b**, which was purified by preparative TLC (Merck, Kieselgel 60 F_{254}, thickness 2 mm, hexane/ethyl acetate/methanol = 6:4:1) (3.10 g, 67%). Oil, $[\alpha]_D$ +34.6 (*c* 1, $CHCl_3$). ^1H-NMR: δ 0.89 (t, 3H, CH_3, J = 7.0), 0.90 (t, 3H, CH_3, J = 7.0), 1.30 (m, 10 H, CH_2), 2.53 (m, 2H, CH_2N), 28.6 (q, 1H, H-6, J = 6.0), 3.65 (dd, 1H, H-1a, $J_{1a,1b}$ = 11.0, $J_{1a,2}$ = 3.8), 3.70 (dd, 1H, H-1b, $J_{1b,1a}$ = 11.0, $J_{1b,2}$ = 2.3), 3.82 (dd, 1H, H-5, $J_{5,6}$ = 6.0, $J_{5,4}$ = 4.0), 3.87 (m, 1H, H-2), 3.97 (dd, 1H, H-3, $J_{3,2}$ = 8.8, $J_{3,4}$ = 4.0), 4.10 (t, 1H, H-4, J = 4.0), 4.50 (d, 1H, PhCHO, J = 12.0), 4.52 (d, 1H, PhCHO, J = 11.5), 4.56 (d, 1H, PhCHO, J = 12.0), 4.66 (d, 1H, PhCHO, J = 11.6), 4.67 (d, 1H, PhCHO, J = 12.0), 4.74 (d, 1H, PhCHO, J = 12.0), 4.78 (d, 1H, PhCHO, J = 11.5), 4.85 (d, 1H, PhCHO, J = 11.6), 7.35 (m, 20H, PhH). ^{13}C NMR: δ 14.59 and 14.69 (2 CH_3); 21.05, 23.61, 29.07, 30.46 and 32.72 (5 CH_2); 47.76

(CH_2N); 59.12 (C-6); 72.75 (C-1); 73.97, 73.97, 74.26 and 74.71 (4 $PhCH_2O$), 72.95, 77.98, 80.04 and 82.52 (C-2, C-3, C-4, C-5). Anal. calcd. for $C_{42}H_{55}NO_5$: C, 77.15; H, 8.48; N, 2.14. Found: C, 77.11; H, 8.52; N, 2.18.

(2*S*,3*R*,4*R*,5*R*,6*S*)-*N*-Butyl-2-benzyloxymethyl-6-butyl-3,4,5-tribenzyloxypiperidine (9b). Compound **8b** (365 mg, 0.56 mmol), dissolved in dry pyridine (4 ml), underwent the cyclization with Tf_2O (1.5 eq). After 2 hrs, the reaction was complete, the reaction mixture was diluted with ethyl acetate (5 ml) and washed with water (3×10 ml portions); the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. Chromatographic purification (9:1) afforded **9b** (167 mg, 47%). Oil, $[\alpha]_D$ +16.2 (*c* 1, $CHCl_3$). ^{1}H-NMR: δ 0.85 (t, 3H, CH_3, J = 7.0), 0.86 (t, 3H, CH_3, J = 7.0), 1.10-2.20 (m, 10H, CH_2), 2.65 (m, 2H, CH_2N), 2.94 (dt, 1H, H-1, $J_{1,2} = J_{1,1"a} = 4.3$, $J_{1,1"b} = 8.5$, determined by selective decoupling experiments), 3.27 (dt, 1H, H-5, $J_{5,6a} = J_{5,6b} = 6.0$, $J_{5,4} = 3.3$), 3.57-3.68 (m, 4H, H-2, H-3, H-6a, H-6b), 3.86 (dd, 1H, H-4, $J_{4,3} = 5.0$, $J_{4,5} = 3.3$), 4.35-4.60 (m, 8H, 4 $PhCH_2O$), 7.35 (m, 20H, PhH). ^{13}C NMR: δ 14.69 (2 CH_3); 21.20, 23.89, 26.67, 27.77, 28.67 (5 CH_2); 49.42 (CH_2N); 58.06 and 58.38 (C-2, C-6); 70.66, 71.89, 72.98, 73.73 and 73.73 (4 $PhCH_2O$, C-1); 73.15, 76.83 and 76.83 (C-3, C-4, C-5). MS/FAB: 635 (M^+). Anal. calcd. for $C_{42}H_{53}NO_4$: C, 79.33; H, 8.40; N, 2.20. Found: C, 79.41; H, 8.35; N, 2.22.

(2*S*,3*R*,4*R*,5*R*,6*S*)-*N*-Butyl-6-butyl-2-hydroxymethyl-3,4,5-trihydroxypiperidine (10b). A solution of compound **9b** (167 mg) dissolved in a mixture of MeOH-ethyl acetate (1:1) was hydrogenated in the presence of HCl 2N (1 eq) and 10% of Pd/C. The reaction was recovered by filtration on a Celite pad and evaporation of the solvent to dryness. Extraction with CH_2Cl_2 of **10b** in aqueous solution was necessary in order to obtain a pure product. Oil, $[\alpha]_D$ + 4.1 (*c* 1, MeOH). ^{1}H-NMR (D_2O, 65 °C): δ 1.39 (t, 3H, CH_3, J = 7.0), 1.43 (t, 3H, CH_3, J = 7.0), 1.86 (m, 8H, CH_2), 2.20 (m, 2H, CH_2), 2.36 (bs, 1H, NH), 3.78 (m, 2H, CH_2N), 3.93 (m, 1H, CHN), 4.14 (bs, 1H, CHN), 4.45-4.70 (5H, CH_2O, H-3, H-4, H-5). ^{13}C NMR: δ 13.67 and 13.84 (2 CH_3); 19.86, 22.95, 22.95, 26.04, 26.31 (5 CH_2); 49.17 (CH_2N); 59.99 (C-1"); 60.31 and 60.66 (C-2, C-6); 66.03, 69.43 and 69.95 (C-3, C-4, C-5). Anal. calcd. for $C_{14}H_{30}ClNO_4$: C, 53.92; H, 9.70; N, 4.49. Found: C, 53.69; H, 9.66; N, 4.21.

(2*R*,3*S*,4*S*,5*S*)-5-Benzylamino-2-3,4-tribenzyloxyhept-6-en-1-ol (13). A solution of 2,3,4-tri-*O*-benzyl-D-ribopyranose **11** (920 mg, 2.19 mmol) and 4Å molecular sieves in dry CH_2Cl_2 (30 ml) was treated with benzylamine (2.4 ml, 21.9 mmol). After 4 hrs the reaction was complete (monitored by TLC); the reaction mixture was filtered on a Celite pad and the solvent and the excess of amine were evaporated under reduced pressure. The unstable ribosylamine **12** (1.11 g) was directly dissolved in dry THF (10 ml) and added to a solution of vinylmagnesium bromide (10 eq) in dry THF (30 ml). After 1 h the reaction was complete; the reaction mixture was quenched with NH_4Cl saturated solution. The organic layer was diluted with CH_2Cl_2 (20 ml), washed with 5% HCl (the minimum amount until the magnesium salts dissolved), $NaHCO_3$ saturated solution (2×50 ml) and water (2×50 ml) to neutrality. The organic phase was then dried over anhydrous Na_2SO_4, filtered and evaporated. Column chromatography (7:3) afforded compound **13** (720 mg, 61% from **11**). Oil, $[\alpha]_D$ = +0.7 (c 1.3, $CHCl_3$). ^{1}H NMR: δ 3.40 (dd, 1H, H-5, $J_{4,5} = 6.7$, $J_{5,6} = 8.0$), 3.53 (d, 1H, PhCHN, J = 13.1), 3.72 (dd, 1H, H-4, $J_{4,5} = 6.7$, $J_{3,4} = 4.5$), 3.79-3.84 (m, 4H, H-1, H-2, $PhCH_2N$), 4.03 (t,

1H, H-3, J = 4.5), 4.55 (s, 2H, $PhCH_2O$), 4.59 (d, 1H, PhCHO, J = 11.0), 4.61 (d, 1H, PhCHO, J = 11.0), 4.70 (d, 1H, PhCHO, J = 11.0), 4.78 (d, 1H, PhCHO, J = 11.0), 5.20 (dd, 1H, H-7a, $J_{7a,6}$ =17.6, $J_{7a,7b}$ = 1.4), 5.22 (dd, 1H, H-7b, $J_{7a,7b}$ = 1.4, $J_{7b,6}$ = 10.0), 5.71 (ddd, 1H, H-6, $J_{6,7a}$ = 17.6, $J_{6,7b}$ = 10.0, $J_{6,5}$ = 8.0), 7.40 (m, 20H, PhH). ^{13}C NMR: δ 51.60 ($PhCH_2N$); 62.33 (C-5); 62.43 (C-1); 72.80, 74.40 and 75.28 (3 $PhCH_2O$); 80.46, 80.81 and 83.29 (C-2, C-3, C-4); 118,99 (C-7); 138.98 (C-6). Anal. calcd. for $C_{35}H_{39}NO_4$: C, 78.18; H, 7.31; N, 2.60. Found: C, 78.24; H, 7.27; N, 2.65.

(2*R*,3*S*,4*R*,5*R*)-*N*-Benzylamino-2-ethenyl-3,4,5-tribenzyloxypiperidine (14). A solution of **13** (400 mg, 0.74 mmol) in dry pyridine (10 ml) was treated with Tf_2O (1.5 eq). After 30 min., the reaction was complete, the reaction mixture was diluted with ethyl acetate (10 ml) and washed with water (2×10 ml); the organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated. Column chromatography (9:1) afforded **14** (270 mg, 70%). Oil, $[\alpha]_D$ = +75.8 (c 1, $CHCl_3$). ^1H NMR: δ 2.67 (dd, 1H, H-6a, $J_{6a,5}$ = 4.7, $J_{6a,6b}$ = 10.8), 2.95 (t, 1H, H-6b, J = 10.8), 3.51 (dd, 1H, H-2, $J_{2,3}$ = 5.5, $J_{2,1'}$ = 10.0), 3.56 (d, 1H, PhCHN, J = 13.4), 3.58 (m, 2H, H-3, H-5), 3.73 (d, 1H, PhCHN, J = 13.4), 4.19 (broad s, 1H, H-4), 4.49 (d, 1H, PhCHO, J = 12.0), 4.51 (s, 2H, $PhCH_2O$), 4.66 (d, 1H, PhCHO, J = 12.0), 4.84 (d, 1H, PhCHO, J = 12.0), 4.92 (d, 1H, PhCHO, J = 12.0), 5.10 (dd, 1H, H-2'a, $J_{2'a,1'}$ = 17.3, $J_{2'a,2'b}$ = 1.9), 5.52 (dd, 1H, H-2'b, $J_{2'b,1'}$ = 10.0, $J_{2'a,2'b}$ = 1.9), 6.58 (dt, 1H, H-1', $J_{1',2'a}$ = 17.3, $J_{1',2'b}$ = $J_{1',2}$ = 10.0), 7.4 (m, 20H, PhH). ^{13}C NMR: δ 46.92 and 59.13 ($PhCH_2N$, C-6); 64.12 (C-2); 71.22, 71.22 and 74.40 (3 $PhCH_2O$); 76.07, 76.95 and 79.56 (C-3, C-4, C-5); 119.92 (C-2'); 134.54 (C-1'). Anal. calcd. for $C_{35}H_{37}NO_3$: C, 80.89; H, 7.18; N, 2.70. Found: C, 80.53; H, 7.26; N, 2.37.

(2*R*,3*S*,4*R*,5*R*)-2-Ethyl-3,4,5-trihydroxypiperidine (15). Hydrogenation of **14** (160 mg) in MeOH (3 ml) and HCl 2N (1 eq), in the presence of 10% Pd/C, gave quantitatively product **15**·HCl (61 mg), after recovering the reaction mixture by filtration on a Celite pad and evaporation of the solvent to dryness. Oil, $[\alpha]_D$ -18.0 (c 1, MeOH). ^1H NMR (D_2O): δ 1.02 (t, 3H, CH_3, J = 7.0), 1.82 (m, 2H, CH_2), 3.17 (broad t, 1H, H-2, J = 6.8), 3.21 (d, 1H, H-6a, J = 13.7), 3.38 (dd, 1H, H-6b, $J_{6a,6b}$ = 13.7, $J_{6a,5}$ = 2.0), 3.80 (broad s, 1H), 4.07 (broad s, 1H), 4.15 (broad s, 1H). ^{13}C NMR (D_2O): δ 11.66 (C-2'), 24.64 (C-1'), 51.58 (C-2), 63.54 (C-6), 70.42, 71.11 and 78.66 (C-3, C-4 and C-5). Anal. calcd. for $C_7H_{16}ClNO_3$: C, 42.54; H, 8.16; N, 7.09. Found: C, 42.57; H, 8.08; N, 7.16.

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REFERENCES

1. (a) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature*, **1987**, *330*, 74; (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong. S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 9229.
2. (a) Bernacki, R. J.; Niedbala, M. J.; Korytnyk, W. *Cancer Metastasis Rev.* **1985**, *4*, 81; (b) Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131; (c) Humphries, M. J., Masumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215
3. See inter alia: (a) Henderson, I.; Laslo, K.; Wong, C-H. *Tetrahedron Lett.* **1994**, *35*, 359; (b) von der Osten, C. H.; Sinskey, A. J.; Barbas, C. F.; Pederson, R. L.; Waon, Y-F.; Wong C-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924; (c) Straub, A.; Effenberger, F.; Fisher, P. *J. Org. Chem.* **1990**, *55*, 3926; (d) Takaoka, Y.; Kajimoto, T.; Wong, C-H. *J. Org. Chem.* **1993**, *58*, 4809; (e) Liu, K. K-C.; Kajiamoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C-H. *J. Org. Chem.* **1991**, *56*, 6280; (f) Kajiamoto, T.; Liu, K. K-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Wong, C-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187;
4. See inter alia: (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Merino, P. *J. Chem. Soc., Chem. Commun.* **1990**, 854; (b) Dondoni, A.; Merino, P.; Perrone, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1576; (c) Burgess, K.; Chaplin, D. A.; Henderson, I. *J. Org. Chem.* **1992**, *57*, 6187; (d) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939.
5. See inter alia: (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165; (b) Furneaux, R. H.; Tyler, P. C.; Whitehouse, L. A. *Tetrahedron Lett.* **1993**, *34*, 3609; (c) Meng, Q.; Hesse, M. *Helv. Chim. Acta*, **1991**, *74*, 445.
6. See inter alia: (a) Furneaux, R. H.; Tyler, P. C.; Whitehouse, L. A. *Tetrahedron Lett.* **1993**, *34*, 3613; (b) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron Lett.* **1988**, *29*, 2871; (b) Fairbanks, A. J.; Carpenter, N. C.; Fleet, G. W.; Ramsden, N. G.; Cenci de Bello, I.; Winchester, B. G.; Al-Daher, S. S.; Nagahashi, G. *Tetrahedron* **1992**, *48*, 3365; (d) Farr, A. R.; Holland, A. K.; Huber, E. W.; Peet, N. P.; Weintraub, P. M. *Tetrahedron* **1994**, *50*, 1033.
7. See inter alia: (a) Streith, J.; Augelmann, G.; Fritz, H.; Strub, H. *Tetrahedron Lett.* **1982**, *18*, 1909; (b) Auberson, Y.; Vogel, P. *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 1498.
8. Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555.
9. (a) Liu, P. S.; Hoeksta, W. J.; King C-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829. (b) Karpas A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. USA*. **1988**, *85*, 9229.
10. Platt, F. M.; Neises, G. R.; Dwek, R. A.; Butters, T. D. *J. Biol. Chem.* **1994**, *269*, 8362.
11. Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181
12. Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun.* **1989**, 298.
13 Dale, M. P.; Ensley, H. E.; Kern, K.; Sastry, K. A. R.; Beyers, L. D. *Biochemistry* **1987**, *167*, 305.

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